GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398

Tel 919 483 2100
www.gsk.com

June 16, 2005

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

SUPPLEMENT TO CITIZEN PETITION

Docket No. 2004P-0239

The undersigned, on behalf of GlaxoSmithKline (GSK), submit this supplement to the above-referenced citizen petition, filed with the Food and Drug Administration (FDA) on May 19, 2004 (the Petition). The Petition requests that FDA complete the process of developing guidance addressing valid bioavailability (BA) and bioequivalence (BE) methods for locally acting nasal spray products, including statistical criteria for the *in vitro* and *in vivo* comparative tests required for a demonstration of bioequivalence. In addition, the Petition requests that FDA refrain from approving abbreviated new drug applications (ANDAs) seeking approval of generic copies of FLONASE® (fluticasone propionate) Nasal Spray until the guidance development process has been completed. (An earlier supplement to the Petition extended this requested relief to BECONASE AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray.)

In further support of the Petition, GSK submits the attached declaration of Jane E. ("Beth") Morgan, Ph.D., an expert statistician employed by GSK (the Declaration). Dr. Morgan has analyzed the publicly available review documents that support an array of generic nasal *solution* products approved by FDA in recent years. FLONASE and BECONASE AQ are formulated as *suspensions*, which pose even greater bioequivalence challenges than products formulated as solutions because the distribution of drug particle size in suspensions cannot be characterized (thus rendering *in vitro* comparisons alone insufficient as a basis for evaluating bioequivalence). To date, no ANDA has been approved for a locally acting nasal product formulated as a suspension. FDA has, however, included both types of

2004P-0239 SUP 2

formulations in its BA/BE guidance development process, and it is clear that ANDAs for both types of formulations will need to show equivalence in various *in vitro* tests as a necessary -- if not sufficient -- condition for documenting bioequivalence.

As recounted in detail in her declaration, Dr. Morgan sought to determine whether the agency has, in reviewing and approving ANDAs for nasal solution products, been applying statistical methods and criteria that are clear and consistent from application to application, and that are aligned with the conventional standards that government and industry statisticians apply in making equivalence assessments. She concludes that they are not, thus reinforcing the importance of defining valid statistical methods and criteria for determining bioequivalence as part of the still incomplete guidance development process.

Most tellingly, Dr. Morgan finds that FDA has generally accepted, as evidence of *in vitro* "equivalence," data and analyses that start from a presumption that a proposed generic product is equivalent to the innovator product, and conclude with that same finding of equivalence unless compelling data to the contrary have emerged. *See* Declaration at ¶¶ 13-21. However, starting with a presumption of equivalence is not the correct statistical approach and does not, statistically, prove equivalence. Even in the context of analyses founded upon this incorrect presumption of equivalence, Dr. Morgan identifies instances in which statistically significant differences between products – *i.e.*, the kind of "compelling data to the contrary" that should overcome a starting premise of equivalence – have apparently been disregarded, without adequate explanation. *See id.* at ¶¶ 22-27.

Even when the agency has been presented with data and analyses that appear to proceed from a more conventional starting point of presumed inequivalence between test and reference products, statistical confidence intervals were not incorporated into the presented data evaluation. Dr. Morgan explains that confidence intervals are indispensable as a means of accounting for the variability of observed data, and conventional statistical practice within government and industry requires their use. *See id.* at ¶¶ 28-30. As part of her analysis, Dr. Morgan cites specific examples where, had FDA applied its standard statistical techniques, a determination of bioequivalence would have been difficult to sustain. *See id.* at ¶¶ 31-36.

Dr. Morgan's overall assessment is that the "lack of statistical regularity in the approvals to date is troubling." *Id.* at ¶ 40. She adds that "the agency and the industry would be well served were FDA to complete the guidance process it began more than five years ago, and publish a clear and validated methodology for

establishing bioequivalence for locally acting nasal spray products ... [including] publication – and adequate opportunity for public comment – of complete proposals for satisfactory statistical methodologies and acceptance criteria." *Id.*

Respectfully submitted,

C. Elaine Jones, Ph.D.
Vice President, US Regulatory Affairs

William M. Zoffer
Vice President, Assistant General Counsel

Attachment

cc: David M. Fox
Brian R. McCormick
Hogan & Hartson LLP